Remarks/Arguments.

By the present amendment, forty-one (41) claims including one (1) independent claim are amended. Nine (9) claims are cancelled hereby. Thirteen (13) new claims are added by amendment. No additional claim fees are payable.

The present amendment is proposed to further clarify that the originally filed clause "means to inhibit agglomeration" is a "step plus function" clause written in satisfaction of 35 U.S.C. §112 paragraph 6.

Claims 14 – 17 and 42 –45 are cancelled herein without prejudice.

No new matter is introduced by the present amendment. Support for the present amendments are set forth herein in the attached "Table of Support." There are no changes in inventorship resulting from the present amendments.

1. Double Patenting

Certain claims in the present application stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting over copending application Serial No. 09/932,500.

As no conflicting claims in 09/932,500 have been allowed at this time, a Terminal Disclaimer would be premature. Moreover, with amendment herein to limit the present claims by recitation of a selective COX-2 inhibitor drug, wherein said drug has at least one property selected from the group consisting of electrostatic, cohesive, low bulk density, low compressibility, and poor flow, said properties conferring upon the composition a tendency to agglomerate," Applicant respectfully submits that the double patenting rejection is overcome without need for a Terminal Disclaimer.

2. Rejections under 35 U.S.C. § 103

Claims 1–3, 10–13, 18-25, 28–41, 46-53, 62-83, and 86-102 are pending in the present Application following amendment herein.

2.1. Rejection over Mizumoto in view of Talley

Claims 1–3, 10–25, 28–53, 62–83 and 86–89 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Mizumoto (U.S. Patent No. 5,576,014) in view of Talley. (U.S. Patent No. 5,760,068). In order to expedite allowance of certain claims herein, this response includes a proposed amendment to Claim 1, *inter alia*. By this amendment,

Applicant believes that the above-cited Examiner's rejection is overcome. .

The Examiner states that Mizumoto teaches (a) a quick-dissolved compressed tablet comprising a saccharide having high moldability and a saccharide having low moldability, a drug, and additive agents; and (b) that the drug can be a non-steroidal anti-inflammatory.

Talley teaches *inter alia*, that celecoxib is a selective cox-2 inhibitor.

The instant specification discloses a process for preparing a quick-dissolving compressed tablet comprising a saccharide having high moldability, a saccharide having low moldability, and a drug with a tendency to agglomerate and that is parecoxib. Additionally, the process of the instant invention "comprises a step for inhibiting agglomeration."

The instant application further discloses certain challenges with using the formulation of Mizumoto when the drug is celecoxib, namely:

> "Celecoxib also presents difficulties as a result of unique physical and chemical characteristics such as electrostatic and cohesive properties, low bulk density, low compressibility and poor flow properties. Due at least in part to these properties, celecoxib crystals tend to segregate and agglomerate together during mixing, resulting in a non-uniformly blended composition containing undesirably large, insoluble aggregates of celecoxib. Therefore, it is difficult to prepare a fast-melt composition containing celecoxib that has the desired blend uniformity for rapid and complete disintegration in the mouth.". [page 5, lines 10-18]

These unique challenges were solved by the instant inventors who teach in the present application:

> "For example, in fluid bed granulation, means to inhibit agglomeration can include addition of a wetting agent, having the effect of providing improved wetting by the granulation fluid of the powder material to be granulated. Alternatively or in addition, means to inhibit agglomeration during granulation can include, for example, pre-wetting the powder material to be granulated, such as by employing an additional, external processor with spraying capacity, and/or using an air distributor plate adapted to increase air flow along the periphery of the granulation bowl" [page 8, lines 7 – 16.
>
> "The wetting agent is present in an amount sufficient to inhibit agglomeration of the drug during preparation of the composition". [page 9, lines 27-28]

> "In a preferred embodiment, compositions of the present invention comprise one or more pharmaceutically acceptable wetting agents. Surfactants, hydrophilic polymers and certain clays can be useful as wetting agents to aid in

> wetting of a hydrophobic drug, such as celecoxib, by the granulation fluid during wet granulation. Where compositions of the present invention are made by the fluid bed granulation process, it is particularly advantageous that the composition contain a wetting agent" [page 23, lines 27-31; page 24, lines 1-2]
>
> "Non-limiting examples of surfactants that can be used as wetting agents in compositions of the present invention include quaternary ammonium compounds, for example . . . Sodium lauryl sulfate is a preferred wetting agent in compositions of the present invention." [page 24, lines 6-23]
>
> "Without being bound by theory, it is believed that, in some situations, glidants, for example talc or silicon dioxide, act to reduce interfacial tension between drug particles, having the effect of inhibiting and/or reducing drug agglomeration, act to decrease electrostatic charges on the surface of drug powders, and act to reduce interparticular friction and surface rugosity of drug particles. See, for example, York (1975) J. Pharm. Sci., 64(7), 1216-1221. Use of a glidant such as silicon dioxide, therefore, can eliminate or reduce the need for a wetting agent in certain instances, for example, when formulating low dose selective cyclooxygenase-2 inhibitory drugs such as valdecoxib."[page 26, line 14-22]

Thus, the instant inventors disclose the challenge of formulating selective COX-2 drugs that tend to agglomerate and invented a solution to the agglomeration, that is, the addition of a step for inhibiting agglomeration in the formulation process. This "inhibitory step for" is fully supported, and "corresponding structure, material [and] acts [are] described in the specification." [35 U.S.C. §112 p6] as recited *supra*. The Examiner cites the general rule that "although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims." However, because the instant Claim 1 contains a proper §112 p6 clause, such a clause must be interpreted by the specification during examination. [*In re Donalson Co.* 16 F.3d 1189 (Fed Cir 1994) (en banc)]. Moreover, in order for the "step for" limitation to read on an accused device (or to be anticipated thereby), the accused device must perform the identical function using the structures disclosed in the specification or equivalents thereof. [*Carrol Touch, Inc. v. Electro Mechanical Systems, Inc.* 15 F.3d 1573 Fed. Cir. 1993).

Accordingly, both the structure and the function of the inhibitory step are limitations of amended Claim 1. Applicant asserts that the prior art, either alone or in combination, fails to teach or disclose the limitations of: a selective COX-2 drug that tends to agglomerate, the inhibitory step, the inhibitory function, and the structure of an inhibitory agent. By failing to teach or suggest all the limitations of Claim 1 as amended herein, the prior art cannot lead to

a conclusion of *prima facie* obviousness of these claims or any claim dependent therefrom (M.P.E.P. § 2143.03).

Withdrawal of the rejection of all claims rejected under 35 U.S.C. § 103(a) as allegedly being obvious e over Mizumoto in view of Talley '068 is therefore respectfully requested.

2.2. Rejection over Mizumoto and Talley in view of Jain.

Claims 1–3, 10–25, 28–53, 62–83 and 86–89 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Mizumoto (U.S. Patent No. 5,576,014) and Talley in view of Jain (U.S. Patent No. 6,316,029)). In order to expedite allowance of certain claims herein, this response includes an amendment to Claim 1, *inter alia*. Thus, Applicant believes that the above-cited Examiner's rejection is now overcome..

The Examiner cites Jain as standing for a rapidly disintegrating solid oral dosage form comprising sodium lauryl sulfate or silicon dioxide. Jain teaches *surface stabilizers,* two of more than 50 such stabilizers disclosed are sodium lauryl sulfate and colloidal silicon dioxide.

In the instant invention, addition of sodium lauryl sulfate as an inhibitory agent is taught as being an illustrative "step for inhibiting agglomeration". The function of the inhibitory step is disclosed as "any measure taken during production of the fast-melt composition to prevent or reduce drug agglomeration or to facilitate separation of existing drug agglomerates.." [page 8, lines 8-9]. Agglomeration is defined by a disclosure of "a preferred embodiment of the invention, an oral fast-melt pharmaceutical composition is provided, comprising a selective cyclooxygenase-2 inhibitory drug of low water solubility dispersed in a matrix comprising . . .." [page 9, lines 21-23]. The term "dispersed," as defined in the instant patent application, "means that the drug is substantially non-agglomerated." [page 9, lines 26-28].

In summary, the instant invention teaches (1) certain inhibitory agents (e.g. sodium lauryl sulfate and/or silicon dioxide), (2) such agents being useful in a process step for inhibiting agglomeration, (3) the process step functioning to inhibit or reduce agglomeration, and (4) a drug that would otherwise promote agglomeration.

In contrast, Jain discloses sodium lauryl sulfate and colloidal silicon dioxide as

surface stabilizers. Jain does not teach or suggest a selective COX-2 inhibitory drug with properties that tend to promote agglomeration. In absence of such a drug (as so limited by Claim 1 of the instant invention), sodium lauryl sulfate (or silicon dioxide) is not serving a function of an inhibitory step. Accordingly, Jain neither teaches the inhibitory step, the inhibitory function, nor the COX-2 inhibitory drug with properties that tend to promote agglomeration. Each of these absent teachings are limitations of the instant Claim 1. Moreover, absent such teachings, there can be no suggestion to use sodium lauryl sulfate or silicon dioxide to modify the teachings of Talley.

Therefore, the combination of Mizumoto and Talley in view of Jain fails to teach or suggest all limitations of the present claims and therefore, no *prima facie* case of obviousness can be sustained (M.P.E.P. § 2143.03). Withdrawal of the rejection of all claims rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Mizumoto and Talley in view of Jain is therefore respectfully requested.

4. Conclusion

Applicant respectfully requests that a timely notice of allowance be issued in this case.

Respectfully submitted,

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Enclosures

Cover Sheet
Fee Transmittal Form
Support Table
Postcard

Support Table

Claim #	limitation	Support
1	wherein the drug has at least one property conferring upon the drug a tendency to agglomerate	"Celecoxib also presents difficulties as a result of unique physical and chemical characteristics such as electrostatic and cohesive properties, low bulk density, low compressibility and poor flow properties. Due at least in part to these properties, celecoxib crystals tend to segregate and agglomerate together during mixing, resulting in a non-uniformly blended composition containing undesirably large, insoluble aggregates of celecoxib. Therefore, it is difficult to prepare a fast-melt composition containing celecoxib that has the desired blend uniformity for rapid and complete disintegration in the mouth.". [page 5, line 10-18] . However, the above-mentioned challenges presented by celecoxib and other cyclooxygenase-2 inhibitory drugs of low water solubility can make fluid bed granulation difficult, particularly as drug loading increases. For example, celecoxib particles have an inherently electrostatic, cohesive nature that promotes agglomeration of the particles. Further, the highly water-insoluble, hydrophobic nature of celecoxib inhibits wetting of these agglomerated drug particles by the granulation fluid during granulation. This lack of wetting inhibits separation of the drug agglomerates. During the process of fluid bed granulation, such agglomeration and poor wetting can act to prevent complete fluidization of the material being granulated and ultimately lead to ineffective granulation. [page 6, line 20-29]
1	a step for inhibiting agglomeration of the drug	In a preferred embodiment, the ,process incorporates means to inhibit agglomeration of the drug. [page 7, line 15-16] The means to inhibit agglomeration incorporated in a process of the invention is any measure taken during production of the fast-melt composition to prevent or reduce drug agglomeration or to facilitate separation of existing drug agglomerates. For example, in fluid bed granulation, means to inhibit agglomeration can include addition of a wetting agent, having the effect of providing improved wetting by the granulation fluid of the powder material to be granulated. Alternatively or in addition, means to inhibit agglomeration during granulation can include, for example, pre-wetting the powder material to be granulated, such as by employing an additional, external processor with spraying capacity, and/or using an air distributor plate adapted to increase air flow along the periphery of the granulation bowl. [page 8, line 7-16
50	wherein said glidant is silicon dioxide and/or talc.	Without being bound by theory, it is believed that, in some situations, glidants, for example talc or silicon dioxide, act to reduce interfacial tension between drug particles, having the effect of inhibiting and/or reducing drug agglomeration, act to decrease electrostatic charges on the surface of drug powders, and act to reduce interparticular friction and surface rugosity of drug particles. [page 26, line 14-18]
90	said agglomeration inhibiting step comprises (i) adding to the composition at least	For example, in fluid bed granulation, means to inhibit agglomeration can include addition of a wetting agent, having the effect of providing improved wetting by the granulation fluid of the powder material to be granulated. [page 8, line 10-12] Without being bound by theory, it is believed that, in some situations, glidants, for example talc or silicon dioxide, act to reduce

	one inhibitory agent selected from the group consisting of wetting agents and glidants and/or (ii) pre-wetting the drug prior to said step (a).	interfacial tension between drug particles, having the effect of inhibiting and/or reducing drug agglomeration, act to decrease electrostatic charges on the surface of drug powders, and act to reduce interparticular friction and surface rugosity of drug particles. [page 26, line 14-18] Alternatively or in addition, means to inhibit agglomeration during granulation can include, for example, pre-wetting the powder material to be granulated, [page 8, line 12-14]
91		Original claim 14
92	wherein the at least one wetting agent is selected from the group consisting of surfactants, hydrophilic polymers, and clays.	In a preferred embodiment, compositions of the present invention comprise one or more pharmaceutically acceptable wetting agents. Surfactants, hydrophilic polymers and certain clays can be useful as wetting agents to aid in wetting of a hydrophobic drug, such as celecoxib, by the granulation fluid during wet granulation. [page 23 line 27 – 30]
93		Original Claim 14
94	the at least one surfactant is selected from the group consisting of quaternary ammonium compounds, dioctyl sodium sulfosuccinate, polyoxyethylene alkylphenyl ethers, polyoxyethylene fatty acid glycerides and oils, polyoxyethylene alkyl ethers, polyoxyethylene fatty acid esters, polyoxyethylene sorbitan esters, propylene glycol fatty acid esters, sodium lauryl sulfate, fatty acids and salts thereof, glyceryl fatty acid esters, sorbitan esters, and tyloxapol.	For example, in fluid bed granulation, means to inhibit agglomeration can include addition of a wetting agent, having the effect of providing improved wetting by the granulation fluid of the powder material to be granulated. [page 8, line 10-12] Non-limiting examples of surfactants that can be used as wetting agents in compositions of the present invention include quaternary ammonium compounds, for example benzalkonium chloride, benzethonium chloride and cetylpyridinium chloride, dioctyl sodium sulfosuccinate, polyoxyethylene alkylphenyl ethers, for example nonoxynol 9, nonoxynol 10, and octoxynol 9, poloxamers (polyoxyethylene and polyoxypropylene block copolymers), polyoxyethylene fatty acid glycerides and oils, for example polyoxyethylene (8) caprylic/capric mono- and diglycerides (*e.g.*, Labrasol™ of Gattefossé), polyoxyethylene (35) castor oil and polyoxyethylene (40) hydrogenated castor oil; polyoxyethylene alkyl ethers, for example polyoxyethylene (20) cetostearyl ether, polyoxyethylene fatty acid esters, for example polyoxyethylene (40) stearate, polyoxyethylene sorbitan esters, for example polysorbate 20 and polysorbate 80 (*e.g.*, Tween™ 80 of ICI), propylene glycol fatty acid esters, for example propylene glycol laurate (*e.g.*, Lauroglycol™ of Gattefossé), sodium lauryl sulfate, fatty acids and salts thereof, for example oleic acid, sodium oleate and triethanolamine oleate, glyceryl fatty acid esters, for example glyceryl monostearate, sorbitan esters, for example sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate and sorbitan monostearate, tyloxapol, and mixtures thereof.[page 24 line 6-22]

95		See new Claim 94
96		See new Claim 90
97	wherein said drug is dispersed in said composition	In a particularly preferred embodiment of the invention, an oral fast-melt pharmaceutical composition is provided, comprising a selective cyclooxygenase-2 inhibitory drug of low water solubility dispersed in a matrix comprising a saccharide of low moldability, a saccharide of high moldability and a wetting agent. Such a composition can be prepared by a process herein described or by any known process. The term "dispersed" in the present context means that the drug is substantially non-agglomerated. The wetting agent is present in an amount sufficient to inhibit agglomeration of the drug during preparation of the composition. [page 9, line 21 – 28]
98	The process of Claim 1 wherein said at least one property is selected from the group consisting of electrostatic, cohesive, low bulk density, low compressibility, and poor flow.	. However, the above-mentioned challenges presented by celecoxib and other cyclooxygenase-2 inhibitory drugs of low water solubility can make fluid bed granulation difficult, particularly as drug loading increases. For example, celecoxib particles have an inherently electrostatic, cohesive nature that promotes agglomeration of the particles. Further, the highly water-insoluble, hydrophobic nature of celecoxib inhibits wetting of these agglomerated drug particles by the granulation fluid during granulation. This lack of wetting inhibits separation of the drug agglomerates. During the process of fluid bed granulation, such agglomeration and poor wetting can act to prevent complete fluidization of the material being granulated and ultimately lead to ineffective granulation. [page 6, line 20-29]
99		See new Claim 1
100		See new Claim 97
101		See new Claim 90
102		See new Claim 92

Claim 1 limitations			
		Mizumoto	Jains
a step of wet granulating a drug			
a step of blending with the drug a saccharide having low moldability		Disclosed	
celecoxib		"non-steroidal anti-inflammatory" disclosed	Anti-inflammatory
Agglomerating drug		NOT Taught	NOT Taught
a step for inhibiting agglomeration of the drug [i]	"inhibitor structure" (e.g. sodium lauryl sulfate or silicon dioxide)	NOT Taught	sodium lauryl sulfate or silicon dioxide
	Perform an agglomeration inhibiting function	NOT performed (function not possible w/o agglomerating drug)	NOT performed (function not possible w/o agglomerating drug) "inhibitor structures taught as surface stabilizers

[i] Moreover, in order for the "step for" limitation to read on an accused device (or to be anticipated thereby)*, the accused device must perform the identical function using the structures disclosed in the specification or equivalents thereof. [*Carrol Touch, Inc. v. Electro Mechanical Systems, Inc.* 15 F.3d 1573 Fed. Cir. 1993).

* parenthetical added per *Peters v Active Manufacturing* 129 U.S. 530 (1889) "That which infringes if later anticipates if earlier."